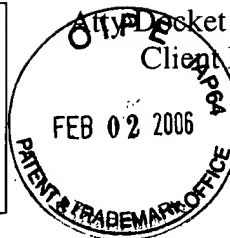


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By: _____

Chianti Applying



File No: 402E-978316US
Client Ref: P0233C6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Phillip W. Berman; Laurence A. Lasky

Application No.: 08/459,141

Filed: 6/2/1995

For: **Immunogenic Composition Based on a Truncated Derivative of a Membrane Bound Protein And Process For Making It**

Examiner: Ulrike Winkler

Art Unit: 1648

REPLY BRIEF

Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

INTRODUCTORY COMMENTS

This Reply Brief is filed in response to the Examiner's Answer, dated November 29, 2005, in the above-identified application. As the two-month period for response expired on January 29, 2006, a Sunday, this Brief, filed on January 30, 2006, is timely.

THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

The only issues on appeal relate to rejections under the judicially created doctrine of obviousness-type double patenting. In particular, claims 10-12, 14-19, 25-29, and 32-41 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 13, 19, and 20 of U.S. Patent No. 4,855,224 (issued August 8, 1989 to Berman *et al.*) in the Final Office Action (dated December 16, 2003), pages 3-4. Upon further reconsideration, the Examiner added claims 1-5, 9, 21, 25, and 26 from the '224 patent to the obviousness-type double patenting rejection. Examiner's Answer, page 3.

Claims 10-23 and 25-41 (*i.e.*, all pending claims) were rejected for obviousness-type double patenting over the claims of the '224 patent noted above in view of Watson *et al.* (Science

1982, 218:381-84)¹ and Dundarov *et al.* (Develop. Biol. Standard. 1982, 52:351-58). Examiners' Answer, page 7.

All pending claims of the present application either recite or refer to a derivative of a membrane polypeptide that:

- (a) *is devoid of the membrane-binding domain* whereby the derivative is free of membrane, *and*
- (b) *has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen . . .*

Claim 13 of the '224 patent recites:

A diagnostic test kit comprising:

- (a) a diagnostic product comprising *a membrane-bound polypeptide with antigenic determinants capable of specifically binding complementary antibodies to herpes simplex virus*, said polypeptide being formed in a recombinant, stable, continuous cell line; and
- (b) a second component comprising either said complementary antibody or anti-antibody capable of specifically binding said complementary antibody.

(Emphasis added.) Claim 19 depends from claim 13 and recites that the "diagnostic product is a truncated, membrane-free derivative of a polypeptide," said derivative *being "devoid of a membrane-binding domain* whereby the derivative is free of said membrane." Claim 20 depends from claim 19 and recites that "the truncated polypeptide is formed by secretion from a recombinant eukaryotic host cell system." Claims 21, 25, and 26, which have been added to the rejections, also depend, directly or indirectly, from claim 13. Claim 21 recites the "diagnostic test kit of claim 13 in which the diagnostic product comprises a membrane-free derivative of the polypeptide in which the polypeptide first is formed functionally associated with a membrane of said recombinant, stable, continuous cell line and then dissolved free from said membrane." Claims 25 and 26 recite that the diagnostic product comprises herpes simplex virus glycoprotein C.

¹ The Final Office Action identified the Watson reference as "Watson et al (Science 1992)." However, in a telephone conference, Examiner Winkler confirmed that reference cited was actually

Claims 1-5, and 9 of the '224 patent, which have been added to the rejections, recite diagnostic products. Claim 1 recites a “diagnostic product comprising ***membrane-bound polypeptide having antigenic determinants capable of specifically binding complementary antibody to herpes simplex virus***, said polypeptide being functionally associated with the membrane of a recombinant, stable, continuous cell line capable of its production.” Claims 2-5 depend from claim 1 and recites particular herpes simplex virus glycoproteins (C or D) or fragments thereof. Claim 19 recites that “said recombinant cell is mammalian.”

Thus, all of the claims of the '224 patent over which the pending claims are rejected relate to polypeptides having “antigenic determinants capable of specifically binding complementary antibody to herpes simplex virus.” By contrast, the claims of the present application require the presence of exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen.

THE EXAMINER'S ANALYSIS

The Examiner's obviousness-type double-patenting analysis improperly disregards the distinction between the pending claims and those of the '224 patent as a result of a failure to consider the claims as a whole and erroneous conclusions concerning the technology at issue. The Examiner's analysis further confuses the issue by focusing on a species described in the specification of the '224 patent, rather than the claims of the '224 patent and by improperly relying on inherency to establish obviousness.

I. The Examiner's analysis fails to consider the claims as a whole.

A double patenting analysis must be based on a comparison of each claim considered as a whole. *See, e.g., General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278-79 (Fed. Cir. 1992) (“Claims must be read as a whole in analyzing a claim of double patenting.”); *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 25 (Fed. Cir. 2000); *Eli Lilly v. Barr Laboratories, Inc.*, 251 F.3d 955, 972 (Fed. Cir. 2001).

Footnote continued from previous page
the 1982 Science article authored by Watson.

The Examiner starts the analysis with the statement that the “patented claims are drawn to diagnostic products, which have the same structure as the instantly claimed immunogenic composition.” Examiner’s Answer, page 4. In fact, the patented claims are drawn to a diagnostic product (claim 1) and a diagnostic test kit (claim 13), that are clearly structurally different from the immunogenic compositions recited in the pending claims. The diagnostic product of claim 1 comprises a polypeptide that is “functionally associated with the membrane.” All the pending claims, by contrast relate, to immunogenic compositions comprising a polypeptide derivative that “is devoid of the membrane-binding domain whereby the derivative is free of membrane.” These structural requirements of claim 1 and the pending claims are not simply different--they are diametrically opposed.

The diagnostic test kit of claim 13 recites two components, one of them a diagnostic product and the other a related antibody. Appellants respectfully submit that an immunogenic composition, of any kind, cannot reasonably be said to have the same structure as “a test kit.” A test kit is simply not something that is injected into the body to elicit an immunogenic response. Moreover, the claimed test kit recites an antibody in addition to the claimed diagnostic product. The Examiner’s conclusion that what is currently claimed is structurally identical to what was previously patented simply ignores the presence of the antibody. The Examiner’s analysis thus suffers from the flaw that it compares the immunogenic composition of the pending claims with an element recited in claim 13 of the ‘224 patent, and not with the claim as whole.

II. The Examiner’s analysis fails to take into account that not all antigenic determinants are neutralizing determinants.

Even if the Examiner were permitted to read elements out of the claims and compare the immunogenic composition of the pending claims with the diagnostic product of claim 13 and its dependent claims, the Examiner’s conclusion that the two are structurally identical is still incorrect. The Examiner’s conclusion appears to be based on the assumption that the same antigenic determinants that bind complementary antibody will also be capable of producing an *in vivo* neutralizing antibody response. In particular, the Examiner states that “the structure of the prior patented ‘diagnostic product’ is that same as that in the present invention, [and therefore] adding the descriptive phrase ‘capable of raising neutralizing antibodies *in vivo*’ does not alter the structure of the composition.” Examiner’s Answer, page 5. This rationale ignores the well-known scientific

reality that only some antigenic determinants are neutralizing determinants. In other words, proteins typically contain multiple sites that bind complementary antibody. These are termed “antigenic determinants” or “epitopes.” Some or one or none of these sites may be capable of eliciting an *in vivo* neutralizing antibody response against a pathogen. Sites that do have this capability, if any, are termed “neutralizing antigenic determinants” or “neutralizing epitopes.” Thus, if a particular protein is shown to have 20 sites that bind complementary antibody, it may be that only one such site is a neutralizing antigenic determinant. If, for example, the neutralizing antigenic determinant is the most amino-terminal antigenic determinant, the requirement that a derivative of the protein be capable of eliciting an *in vivo* neutralizing antibody response dictates that the derivative must contain that amino-terminal neutralizing determinant. By contrast, the requirement that the derivative be capable of binding complementary antibody simply requires that the derivative contain at least one of the 20 antigenic determinants scattered throughout the protein. This hypothetical makes it absolutely clear that the genus of derivatives capable of eliciting an *in vivo* neutralizing response defines a structurally different set of molecules than that defined by the genus of derivatives capable of binding complementary antibody.

III. The Examiner’s analysis improperly focuses on a species described in the ‘224 specification, rather than on the claims of the ‘224 patent.

The most fundamental error of the Examiner’s analysis is that, rather than focusing on the invention defined by the claims, the Examiner has focused on a particular species described in the specification of the ‘224 patent. This species contains “antigenic determinants capable of specifically binding complementary antibodies to herpes simplex virus,” as recited in the claims of the ‘224 patent and also contains “exposed antigenic determinants capable of raising neutralizing antibodies against *in vivo* challenge by the pathogen,” as recited in the pending claims. Appellants respectfully submit that the disclosure of this species in the ‘224 patent is irrelevant to the question of whether the immunogenic composition recited in the pending claims is an obvious variant of the diagnostic product or test kit of the ‘224 patent. *In re Kaplan*, 789 F.2d 1574 (Fed. Cir. 1986), discussed in the Appeal Brief, makes that point abundantly clear. In that case, a claim rejected for obviousness-type double patenting related to a chemical process carried out in a solvent mixture of tetraglyme and sulfolane. *Id.* at 1575. The reference (Kaplan) patent claimed the same process carried out “in the presence of an organic solvent.” *Id.* The specification of the Kaplan patent

included Example 45, which disclosed carrying out the process in a mixture of tetraglyme and sulfolane. *Id.* In the *Kaplan* case, the species recited in the rejected claim was within the scope of the genus claimed in the reference patent and was specifically disclosed in the specification of the reference patent. Nevertheless, the Federal Circuit reversed the double-patenting rejection. *Id.* at 1580 (citations omitted). In other words, the Federal Circuit reversed a double patenting rejection on facts similar to those on which the Examiner relies to establish a double patenting rejection.

IV. The Examiner's analysis improperly relies on inherency in an effort to establish obviousness.

The Examiner notes that the "mere recitation of newly-discovered function (capable of raising neutralizing antibodies) or a property, inherently possessed by things in the prior art, does not cause the claim drawn to those things to distinguish over the prior art." Examiner's Answer, page 6 (citations omitted). This statement, while true, is irrelevant because, as explained above, the capability of raising neutralizing antibodies defines a genus of membrane-free derivatives with a structure that confers this capability. This genus differs from the genus of such derivatives that need only be capable of binding complementary antibody. In other words, the claim element that the Examiner views as merely functional (defining a new property) defines a set of molecules with particular structures.

However, the Examiner's analysis is also flawed because obviousness cannot be predicated on inherency. That a truncated gD exemplifying the polypeptide derivative recited in claim 19 of the '224 patent was inherently capable of eliciting an *in vivo* neutralizing antibody response is irrelevant to the present inquiry because one skilled in the art would not have known this from reading the portions of the specification that support the claims 13, 19, and 20 of the '224 patent. Properties of the truncated gD that are inherent, but neither disclosed nor suggested in any portion of the '224 specification that can be considered, cannot be relied upon to establish obviousness.

The Examiner notes that "[a] generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus if the prior art discloses a species falling within the claimed genus." Examiner's Answer, page 17. This statement misses the point that the prior art being applied in an obviousness-type double-patenting rejection is what is recited in the reference patent's claims, not what is disclosed in the reference patent's specification. The

Examiner's statement would be relevant only if the '224 patent claimed a species that was within the scope of any of the pending claims. It does not. The pending claims relate to immunogenic compositions comprising a membrane-free derivative of a membrane protein that has exposed antigenic determinants capable of eliciting an in vivo neutralizing antibody response. This genus does not encompass the diagnostic product of claim 1 of the '224 patent, which (1) is functionally associated with a membrane, and (2) need only contain antigenic determinants capable of binding complementary antibody. Furthermore, the genus of the pending claims does not encompass the diagnostic test kit of claim 13 of '224 patent, which (1) is a test kit, rather than an immunogenic composition, and (2) need only contain antigenic determinants capable of binding complementary antibody. Instead of having a genus-species relationship, these claims define different genres.

In the present case, it appears that the Examiner believes that the pending claims cannot be issued in the absence of a terminal disclaimer over the '224 patent because pending claim 10, for example, reads on an immunogenic composition comprising the truncated gD exemplified in the application and claim 19 of the '224 patent reads on a test kit containing this same protein. See Examiner's Answer, pages 17 and 21. However, it is well-settled that it is legally irrelevant to a double-patenting analysis whether certain conduct would be "dominated" by two patents. See, e.g., *In re Kaplan*, 789 F.2d 1574, 1577 (Fed. Cir. 1986) ("Domination is an irrelevant fact.") Furthermore, "it is elementary that readability of a claim on the subject matter of another claim (domination) is neither determinative of the double patenting issue nor demonstrative that claims are directed to the same invention." *In re Sarett*, 327 F.2d 1005, 1014 (C.C.P.A. 1964); see also *General Foods Corp.*, 972 at 1278-79.

THE PROPER ANALYSIS

Appellants respectfully submit that the application of the proper standards makes the obviousness-type double patenting analysis in the present case a simple matter and leads inevitably to the conclusion that the pending claims cannot be rejected for obviousness-type double patenting over the cited claims of the '224 patent.

I. The governing law: *In re Vogel* and *In re Kaplan*

The question to be answered in analyzing obviousness-type double patenting is: "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" *In re Vogel*, 422, 441 F.2d 438 (C.C.P.A. 1969). In answering this question,

“only the disclosure of the invention claimed in the patent may be examined.” *Id.* *In re Kaplan* establishes that any disclosure of the reference patent that is not necessary to provide support for the cited claims of the reference patent must be disregarded. *See In re Kaplan*, 789 F.2d 1574, 1580 (Fed. Cir. 1986). Applying these principles to the present case, any statements in the ‘224 specification relating to the ability of any disclosed polypeptide to elicit a neutralizing antibody response are unnecessary to support the ‘224 claims, which require only the ability to bind complementary antibody. Under *Vogel* and *Kaplan*, such statements cannot be considered in determining whether the pending claims recite obvious variants of the inventions recited in the ‘224 claims.

Accordingly, the proper analysis of obviousness-type double-patenting entails determining whether it would be obvious to modify the diagnostic product of ‘224 claims 1-5, 9, 21, 24, or 26, or the diagnostic test kit of ‘224 claims 13, 19, or 20. For the purpose of this analysis, inherent properties of the polypeptides at issue cannot be considered in determining obviousness because, as the Federal Circuit stated in *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993):

“That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.”

Id. at 1534 (citation omitted).

Thus, in determining whether it would be obvious to modify the diagnostic product of claims 1-5, 9, 21, 24, or 26, or the diagnostic test kit of claims 13, 19, or 20 to arrive at the claimed immunogenic composition, the ‘224 specification’s disclosure that a truncated gD lacking the membrane-binding domain is capable of eliciting a neutralizing antibody response cannot be considered. That this capability is inherent in a polypeptide that is one example of the diagnostic product recited in claim 19 of the ‘224 patent is not only not determinative of the obviousness-type double patenting issue, as the Examiner argues, but this fact is not even relevant to the determination.

For simplicity, only independent claims 1 and 13 are discussed below, as Appellants submit that a consideration of these claims alone is sufficient to establish that the pending claims are patentably distinct from diagnostic product and test kit of the ‘224 patent.

II. The pending claims are patentably distinct from the diagnostic product of claims 1-5, 9, 21, 25, and 26 of the '224 patent.

Claim 1 of the '224 patent recites a "diagnostic product comprising *membrane-bound polypeptide having antigenic determinants capable of specifically binding complementary antibody to herpes simplex virus*, said polypeptide being functionally associated with the membrane of a recombinant, stable, continuous cell line capable of its production."

The pending claims relate to an immunogenic composition comprising a truncated derivative of a membrane polypeptide that is "devoid of the membrane-binding domain whereby the derivative is free of membrane." Furthermore, the pending claims relate to a different genus of polypeptides in that the pending claims require the derivative to have "exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by [a] . . . pathogen."

Neither any part of the '224 patent that may properly be considered nor any of the secondary references provides any teaching or suggestion of a truncated derivative of a membrane polypeptide that lacks the membrane-binding domain and retains the ability generate an antibody response of any kind, which is, of course, the most fundamental requirement for "an immunogenic composition," as recited in the pending claims. As is well-known in the art of immunology, the capability of binding complementary antibody is different from the capability of eliciting antibodies of any type. Many molecules, termed "haptens," are incapable of eliciting an immune response unless they are conjugated to an immunogenic carrier. Haptens can, however, bind to complementary antibodies raised against a hapten-carrier conjugate. The ability of whole herpes simplex virus (Dundarov) or glycoproteins that retain the membrane-binding domain (Watson) to raise antibody responses is simply irrelevant to whether the claimed truncated derivative would contain the proper sequences and have the proper secondary structure to elicit a similar response.

In the absence of any hint of this capability, one skilled in the art would have no motivation to truncate the polypeptide of claim 1 of the '224 patent to remove the membrane-binding domain, especially when claim 1 teaches that the polypeptide is "functionally associated with the membrane." Nor would one skilled in the art have any motivation to produce a truncated derivative that retains the ability to elicit an *in vivo* neutralizing antibody response. As discussed in detail above, a truncated derivative that retains this ability does not necessarily have the same structure as a truncated derivative that merely retains the ability to bind complementary antibody.

The portions of the record available for consideration are simply silent as to the requirements for eliciting an *in vivo* neutralizing antibody response. Thus, there is no motivation for modifying the diagnostic product of claim 1 to arrive at the claimed immunogenic composition, nor is there any reasonable expectation of success in doing so.

Because the record fails to establish that it would be obvious to modify the diagnostic product of claims 1-5, 9, 21, 25, and 26 of the '224 patent to arrive at the claimed immunogenic composition, the pending claims are patentably distinct from these claims, whether taken alone or in combination with Watson and Dundarov.

III. The pending claims are patentably distinct from the diagnostic test kit of claims 13, 19, and 20 of the '224 patent.

Claim 13 of the '224 recites a diagnostic test kit. The Examiner claims that no modification of the diagnostic test kit of claims 13, 19, and 20 is necessary to arrive at the claimed immunogenic composition because the pending claims are open-ended comprising claims. Examiner's Answer, page 16. Appellants respectfully submit that "test kits" are not administered as immunogens. The Examiner is not free to disregard claim language in the cited claims in order to argue that the pending claims encompass the diagnostic test kit claims. The Examiner believes that the pending claims encompass the test kit of claim 13 because the two recited components of the test kit are a polypeptide (the diagnostic product) and an antibody, which the Examiner alleges would both be expected to elicit an antibody response. But the Examiner has provided no rationale as to why one skilled in the art would combine these components in a single immunogenic composition, which would require one skilled in the art to ignore the context (diagnosis) in which the kit of claim 13 is to be used.

Furthermore, the Examiner's analysis falls into the trap of viewing these claims as relating to individual polypeptides that have the same structure. However, the claims relate to two different genres of polypeptides, namely those that bind complementary antibody and those that elicit a neutralizing antibody response. As explained above, the structural requirements for these two groups of polypeptides are different. The disclosure of truncated derivatives of a membrane polypeptide that are capable of binding complementary antibody and therefore useful for diagnostic purposes would simply not lead one skilled in the art, without more, to truncated derivatives that lack the membrane binding domain, yet retain the determinants required to elicit an *in vivo*

neutralizing antibody response. The parts of the record that are available for consideration contain no indication that the production of such derivatives was even possible.

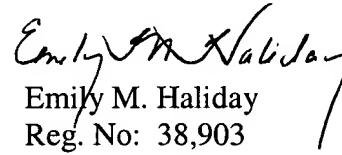
Thus, the record provides no reason for modifying the diagnostic test kit of claims 13, 19, and 20 of the '224 patent to arrive at the claimed immunogenic composition, nor any reasonable expectation of success in doing so. Accordingly, the pending claims are patentably distinct from these claims, whether taken alone or in combination with Watson and Dundarov.

CONCLUSION

In view of the foregoing, reversal of the outstanding rejections is respectfully requested.

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